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PATENT
Attorney Docket No.: ROCH-001DIV
(R0058C-DIV)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:	Examiner: Nirmal Singh Basi
Paul David Cannon et al.	Technology Unit: 1600
Application No.: 10/052,664	Art Unit: 1646
Filed: January 17, 2002	Reply Brief
For: HUMAN INTESTINAL NPT2B	
Assignee: Roche Palo Alto LLC	

Board of Patent Appeals and Interference
Alexandria, VA 22313-1450

REPLY BRIEF (37 CFR §1.193)

This is a Reply Brief to the Examiner's Answer mailed January 13, 2005, by the U.S. Patent and Trademark Office (USPTO), in response to the Appeal Brief filed by Appellants on October 20, 2004 in the above referenced patent application. Jurisdiction over this Appeal resides in the Board of Patent Appeals and Interferences (the Board) under 35 USC § 134. Appellants do not request an oral hearing.

Rejection under 35 USC § 101 for "lack of utility is a question of fact." *In re Swartz* 232 F.3d 862, 56 USPQ2d 1703 (Fed. Cir. 2000). In sustaining the utility rejection, the Examiner's Answer displays four fundamental errors in addressing the facts of this particular case. These errors are: a) misapprehension of the facts relating to the claimed Npt2B polypeptide; b) disregard of the factual evidence provided by Appellants; c) misstatement of the facts in the field of art; and d) misstatement of factual statements contained in the Specification and in the Appeal Brief. Each error is discussed in detail below.

Misapprehension of the facts relating to the claimed polypeptide

First, the claimed Npt2B protein is not an "orphan protein" as asserted by the Examiner (see, e.g., Examiner's Answer at page 6, line 13). An orphan protein is a protein that has no known function. In contrast, however, Npt2B has a **known** function: it transports inorganic phosphate ("Pi") from the intestinal lumen into intestinal epithelial cells, and co-transports sodium (Na^+). It does not require any other ligand for activity. This activity is stated in the Specification at page 4, lines 19-24, and evidence confirming this activity was provided by the Declaration under 37 CFR § 1.132 by Suryanarayana Sankuratri , filed on February 23, 2004 ("Declaration").

Second, the Examiner is apparently under the misapprehension that it is necessary to correlate a disease state with a **dysfunctional** form of the claimed protein (see, e.g., Examiner's Answer at page 5, lines 16-18; page 6, line 2; page 23, line 2). This, however, is not necessary for the practice of Appellants' invention. Appellants instead find that there is utility in inhibition or stimulation of the natural, active Npt2B protein, just as many analgesics inhibit the normal function of receptors or enzymes involved in the signal chain that results in the perception of pain. Because Npt2B is uniquely situated to control absorption of phosphate from the diet, modulation of Npt2B activity is capable of affecting the amount of phosphate that is absorbed. Thus, in diseases or syndromes that are characterized by excessive (or inadequate) levels of phosphate, modulation of Npt2B activity will be therapeutic. For example, where renal failure causes hyperphosphatemia, an Npt2B inhibitor can reduce the amount of phsophate absorbed,

and thus alleviate that symptom (see, e.g., Specification at page 27, lines 27-29). No dysfunction in Npt2B itself is required: one can treat conditions of too much or too little phosphate that are not due to a dysfunctional Npt2B, just as one can treat pain or inflammation that are not due to a dysfunctional pain receptor.

Disregard of factual evidence provided by Appellants

The Examiner has consistently ignored the evidence provided by Appellants, most notably, the evidence contained in the Declaration of Suryanarayana Sankuratri, filed on February 23, 2004, which describes expression of the protein, and presents data verifying the phosphate transporting activity claimed in the Specification which proves that the disclosure in the Specification was **fully enabled** when filed. The use of the Declaration in this case is analogous to the use of the Michael Kluge declaration in *In re Brana,* 51 F.3d 1560, 1566, 34 USPQ 2d 1436, 1441 (Fed. Cir. 1995) in that the data presented was used not to **identify** a utility but to **substantiate** utility already asserted in the specification. The relevant wording in *In re Brana* was set forth in the Appeal Brief (page 14, lines 21-26) but is repeated here because the Examiner's Answer did not address this issue at all:

> "Enablement, or utility is determined as of the application filing date. *In re Glass*, 492 F.2d 1228, 1232, 181 USPQ 31, 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi*, 439 F.2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, **but instead goes to prove that the disclosure was in fact enabling when filed** (i.e. demonstrated utility)." (*In re Brana*, 34 USPQ2d at 1441, emphasis added.)

The Examiner's reason for ignoring the evidence in the Declaration, which is "in the instant case, post-filing art cannot be used to **establish** [emphasis added] utility because the results of the said art were not known at the time of filing of instant application" (Examiner's Answer at page 23, lines 18-20), is contradictory both to the facts around this present case and to law.

Also, as set forth in the Specification at page 28 lines 14-15, Appellants confirmed by RT-PCR that Npt2B is expressed in the small intestine. Appellants have also provided evidence from recent review articles (7-8) that no other type II sodium phosphate co-transporter has been found to be expressed in the intestine. This **fact** demonstrates the unique function of Npt2B and that its utility does not rest solely on homology arguments, as asserted by the Examiner throughout the Examiner's Answer. However, the Examiner apparently believes that the fact that Npt2B was first identified by virtue of its homology with other sodium phosphate co-transporters renders all other information irrelevant.

Finally, Appellants cited three reference papers in the Appeal Brief (page 11, line 8 to page 12, line 6) that provide evidence of the appropriate measure of the general knowledge in the area of type IIb sodium phosphate co-transporters at the time of filing. Hilfiker et al. (1) published in November, 1998, described the cloning of mouse Npt2B and was the first paper to classify the type II sodium phosphate co-transporters into the "type IIa" family, represented by the renal isoforms and the "type IIb" family, represented by the intestinal isoforms, which includes Npt2B. Feild et al. (2) and Xu et al. (3) both described the cloning of human Npt2B, and were published three months and ten months after Appellants' priority date. However, case law has stated that the "court has approved use of later publications as evidence of the state of art *existing on the filing date* of an application." *In re Hogan and Banks* 559 F.2d 595, 605, 194 USPQ 527, 537 (CCPA 1977). All three papers describe their proteins (which have 78.8%, 99.7% and 99.9% sequence identity to the Npt2B polypeptide of Claim 1) as intestinal or type IIb sodium phosphate co-transporter. Thus Appellants have provided evidence that at the time of filing, one skilled in the art would have no doubt that Npt2B is an intestinal sodium phosphate co-transporter and that it is a critical protein in regulating phosphate absorption from the intestine. Therefore the artisan would consider the utilities asserted in the Specification as being specific, substantial and credible.

The factual evidence provided in these papers were ignored in the Examiner's Answer which, instead, relied upon three generic review articles regarding computational genomics (4-6) in

support of his position that the utility of a protein cannot be implicated solely from homology, and that such must be true also for Npt2B. It is important to note that none of the references cited by the Examiner make any mention of sodium phosphate co-transporters. Therefore the following statements in the Examiner's Answer have no factual support:

> ... the art does not provide a teaching stating that all members of the family of sodium phosphate co-transporters necessarily must have the same effects, have the same ligands or are involved in the same disease states. In fact **the art discloses evidence to the contrary** [emphasis added]." (Examiner's Answer at page 7, lines 4-7)
>
> In summary the references discussed above disclose the unpredictability of assigning function to a particular protein based on homology, **especially one that belongs to the family** (sic) **sodium phosphate co-transporter** [emphasis added]" (Examiner's Answer at page 9, lines 8-11)

Furthermore, the central theme from the references cited by Examiner is **not** that function cannot be predicted solely by homology but that function **may not necessarily be** predictable solely from sequence homology. I.e., in some cases, function **is** successfully predicted solely on the basis of homology. The Examiner has provided no example of a case where a protein predicted by sequence homology to be a type II sodium phosphate co-transporter was, in fact, not such a protein, and Appellants are not aware of any such case. Thus, by drawing an inaccurate conclusion from his own references, and by ignoring the references cited by Appellants which provide a preponderance of evidence to the contrary, the Examiner continues to argue as if there would still be doubts in the mind of one of ordinary skill in the art as to the function and utility of Npt2B and to justify the rejection under 35 USC § 101.

Misstatements of the facts in the field of art

In the Appeal Brief, Appellants cited several misstatements made by the Examiner in the two Office Actions that have no factual support and are contrary to general knowledge concerning type II sodium phosphate co-transporters (Appeal Brief at pages 9-11). Many of the same misstatements also appear in the Examiner's Answer, and they can be divided into three main

categories. The first category pertains to Examiner's descriptions of the "family" of sodium phosphate co-transporters. Some of these misstatements include:

> "Members of the sodium phosphate co-transporter family are also **highly divergent** in their **effects** and **ligand specificity**. The outcome of the **cellular signaling effect** varies depending on the specific sodium phosphate co-transporter and the **substrate** activating said cotransporter." [all emphases added] (Examiner's Answer at page 4, lines 14-17)

> "The **superfamily** of sodium phosphate co-transporters is highly **divergent** in their **effects** and **compound specificity**. The utility of the claimed sodium phosphate co-transporter cannot be deduced solely from its homology to known sodium phosphate co-transporters or their protein domains because the art does not provide a teaching that all members of the family of sodium phosphate co-transporters necessarily have the **same effects, the same ligands and are involved in the same disease states**." [all emphases added] (Examiner's Answer at page 23, lines 3-9)

No factual support is provided for these statements nor for other statements in the Examiner's Answer describing the "family" of sodium phosphate co-transporters found at page 6, line 22-page 7, line 1; at page 9, lines 8-11; at page 12, lines 1-3; and at page 14, lines 6-8. In contrast, Appellants have always classified Npt2B as belonging to the **type II** family of sodium phosphate co-transporter (see e.g. Specification at page 4, line 19) which, based on the most recent review article in the field (8), consists of only three members (and not some "superfamily" as alleged by Examiner). All members of the type II family exhibit the activity of transporting phosphate into the cell that expresses the protein, in response to sodium concentration. Furthermore, type II sodium phosphate co-transporters do not require other substrates or ligands for activity and, unlike cell-surface receptors, are not known to be involved in cellular signaling. Thus the Examiner's statements have misstated facts that are known about type II sodium phosphate co-transporters.

The second category of misstatements pertains to the Examiner's descriptions of the utilities of Npt2B which are incorrect due to the mistaken notion that Npt2B is an orphan protein (addressed above) and therefore has no specific and unique function. Two such examples are shown below:

> "All members of the sodium phosphate co-transporter protein family have a utility in selectively screening of candidate drugs that target sodium phosphate co-transporters. However, for a utility to be 'well-established' it must be specific, substantial and credible. In this case all sodium phosphate co-transporters are in some combination useful in selective screening of candidate drugs that target sodium phosphate co-transporter and in toxicology testing;" (Examiner's Answer at page 9, lines 14-20)

> "The inclusion in the family of sodium phosphate co-transporter does not constitute either a specific and substantial asserted utility or a well-established utility for the claimed Npt2B polypeptide. This is analogous to the reasoning that all proteins/nucleic acids of sodium phosphate co-transporter proteins can be used as markers on a gel." (Examiner's Answer at page 22, lines 15-18)

Other examples of misstatements regarding the utilities of Npt2B appear on pages 25-28, where the Examiner argues that use of the Npt2B polypeptide as a screening tool, an immunogen to generate antibodies, and in gene therapy are not specific, substantial and credible, or well-established based upon the **mistaken notion** by the Examiner that Npt2B itself has no specific substantial and credible or well-established function and utility. The facts, however, indicate otherwise.

Appellants' claimed protein is immediately useful for purposes of screening for modulators of phosphate transporter activity. This utility is "specific and substantial." It is "specific" in that using Npt2B as a screening target will identify drug candidates that specifically modulate Npt2B, rather than other proteins.[1] This utility is "substantial" because phosphate must be transported from the intestinal lumen across the epithelium in order to be absorbed from the diet, and as Npt2B is the sole known intestinal phosphate transporter, modulation of its activity is capable of regulating phosphate absorption by the entire body. Thus, screening drug candidates for modulators of Npt2B is not merely an empty exercise, nor for academic interest alone, but has immediate commercial applicability.[2] Further, this utility is credible: the Examiner has presented

[1] It should be noted that the Examiner's assertion that this activity is instead general and not specific is diametrically opposed to the Examiner's repeated assertion that the family of sodium phosphate transporter proteins is diverse and has no known common activity (see, e.g., Examiner's Answer at page 12, lines 13-16).

[2] Appellants do not here assert that a particular *drug* is thus enabled: however, Appellants point out that the right to screen a target has immediate commercial potential, e.g., for licensing to pharmaceutical companies. Consider, for

no reason why one of ordinary skill in the art would fail to believe that Npt2B is useful as a screening target, nor are Appellants aware of any such reason.

Appellants' claimed protein is also independently useful as an antigen for the preparation of antibodies. This utility is also specific and substantial. It is "specific" to Npt2B, because the proper generation of antibodies that specifically bind Npt2B will result in antibodies that specifically bind only to Npt2B, and not to other proteins or antigens. This utility is "substantial" because, inter alia, such antibodies can be used as inhibitors of Npt2B directly, and thus are potential drug candidates with obvious utility, as discussed above. Such antibodies are also useful for other purposes, for example detecting the expression (or absence of expression) of Npt2B, for labeling and sorting cells that express Npt2B, and the like. The Examiner has presented no reason for doubting the utility of Npt2B used as an antigen to prepare specific antibodies, nor are Appellants aware of any such reason: thus, this utility is also credible.

Further, there is no basis for the Examiner's assertion that one must describe "the family of sodium phosphate co-transporter in enough detail to show" that the claimed protein has substantial use (Examiner's Answer at page 14, lines 4-6). Appellants have established utility for the claimed protein directly, by demonstrating its activity in an art-recognized host cell (CHO), and do not require detailed comparison to a family of proteins to demonstrate activity.

In addition, the Examiner's statement on page 20 lines 15-18 of the Examiner's Answer that "the specific function of Npt2B **cannot** [emphasis added] be correlated with other known ion transporters since no other type II human intestinal sodium phosphate co-transporters were known in the art at the time of filing instant application" makes an incorrect inference. At the time of filing, mouse (1), bovine (10), Xenopus (11) and flounder (12) type IIb intestinal sodium phosphate co-transporters were already known, as well as the human type IIa renal sodium phosphate co-transporter (13). Thus when Appellants isolated the Npt2B polypeptide of the

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example, the revenues that Chiron Corp. has extracted from other companies for rights to screen various HCV proteins for inhibitors.

claimed invention from human intestine and demonstrated that it resembles the type IIb co-transporters of non-human species more closely than it does the human type IIa co-transporter (see Specification Experimental Section A page 28-29), it was entirely reasonable to correlate the function of Npt2B with the other known type IIb co-transporters.

The third category of misstatements which have no factual support in the knowledge in the field of type II sodium phosphate transporters pertains to the Examiner's description of disease conditions associated with Npt2B. Some examples are:

> "The limited disclosure of a polypeptide, which has been classified as a human type II sodium phosphate co-transporter, **cannot** [emphasis added] be used to establish utility of claimed polypeptide to treat a variety of diseases associated with Pi/Na transport." (Examiner's Answer at page 21, lines 18-21)
>
> "It is also not clear how the claimed polypeptide can be simultaneously specific for both disease states that are characterized by abnormally high phosphate absorption and disease states characterized by abnormally low phosphate absorption." (Examiner's Answer at page 24, lines 9-11)

The first misstatement by the Examiner is fully contradicted by the article by Peerce et al. (9) cited in the Appeal Brief which states that "a pharmacological method of reducing intestinal phosphate absorption may provide a more palatable approach to reducing serum phosphate and may slow the progression of moderate chronic renal failure to end-stage renal failure." (Appeal Brief at page 12, lines 14-17) and further describes the utility of an inhibitor of the Na^+/phosphate cotransporter, i.e. Npt2B, to accomplish this. The second misstatement is easily contradicted by the fact that Npt2B is uniquely situated to control the absorption of phosphate from the diet and that modulation of Npt2B activity can be therapeutic in diseases or syndromes that are characterized by either excessive or inadequate levels of phosphate in serum. Furthermore, it is not unusual for a target protein to be therapeutic when it is either stimulated or inhibited. For example, agonists of the $alpha_1$ adrenergic receptor are known to be effective in treating nasal congestion, whereas antagonists of the same $alpha_1$ adrenergic receptor are effective treatment for hypertension and for benign prostatic hyperplasia.

Misstatement of factual statements contained in the Specification and in the Appeal Brief

In the Appeal Brief, Appellants cited several misstatements by the Examiner in the Office Actions that contradict specific statements in the Specification (Appeal Brief at pages 8-9). Many of the same misstatements appear in the Examiner's Answer (see e.g. Examiner's Answer at page 5, lines 12-14 and at page 6, lines 8-11) and these need not be addressed again. Instead, new misstatements in the Examiner's Answer to statements either in the Specification or in the Appeal Brief are cited here.

The Examiner states on page 9, line 20 to page 10, line 1 of the Examiner's Answer that "the particulars of screening for candidate drugs that target the claimed sodium phosphate co-transporters, and in toxicology testing **are not disclosed** [emphasis added] in the instant specification. None of the candidate drugs, toxic substances or the susceptible organ systems are identified." However, this ignores Appellants' description of **exactly** this assay in the Specification (see, for example, page 17, lines 9-21 and page 30, lines 4-19). Candidate drugs are discussed at page 18, lines 9-19, and at page 18, line 29 to page 19, line 5, although it should be noted that no disclosure of candidate drugs is necessary to enable a method of screening: one of ordinary skill in the art knows where to obtain molecules for screening, and the patentability of the present invention does not depend on the selection of any particular molecule to be screened. It should further be noted that antibodies specific for Npt2B are immediate candidate Npt2B inhibitors (see page 21, line 3), and that preparation of such antibodies is disclosed in the Specification at page 21, line 14 through page 22, line 12. As the protein is expressed in the intestine, Appellants submit that the "susceptible organ system" is obvious.

On page 20, lines 7-10 of Examiner's Answer, the Examiner contends that "the statement, 'the specification discloses a specific function for the claimed invention, which is a human type II sodium phosphate co-transporter that provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells' is not fully supported by the specification." The facts reveal the contrary. The Specification states on page 4 lines 19-24, that

"Npt2B is a **type II sodium phosphate co-transporter**. In its native environment, Npt2B is a co-transporter of sodium cation and phosphate anion. Npt2B is expressed, among other locations, on the surface of intestinal epithelial cells, i.e. on the apical or intestinal luminal side of the epithelial cells, and therefore **provides for the transport of sodium and phosphate ions from the intestinal lumen into the intestinal epithelial cells**." Also, page 4 line 9 of the Specification clearly states that Npt2B is "a novel **human** sodium phosphate co-transporter." Thus the statement in question, although not recited verbatim in the Specification, is nevertheless fully supported by the specification, as shown above.

From page 21, line 21 to page 22, line 2 of the Examiner's Answer, the Examiner states, "...there is no experimental data to support the statement that the claimed sodium phosphate co-transporter is responsible for absorption and uptake of phosphate in the intestine." Appellants note that this statement is contradicted by the disclosure in the Specification (i.e. detection of Npt2B mRNA in the human intestine in Experimental Section A, page 29 lines 10-13; expression of Npt2B in mammalian cells in Experimental Section B, page 30 lines 4-19) and in the Declaration.

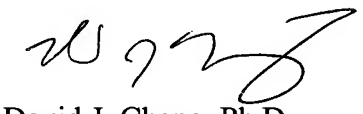
The Examiner states on page 25 lines 19-22 that "Appellants' argue the claimed sodium phosphate co-transporter protein is useful as a screening tool and **that all members of the sodium phosphate co-transporter protein family have utility in the selective screening of candidate drugs that target sodium phosphate co-transporters**." Appellants point out that the bolded portion of the statement was contained in the Appeal Brief (page 10, 4th paragraph) as one example of numerous *misstatements* made by the Examiner that appeared in the Office Actions which have no factual support in the knowledge in the field of Type II sodium phosphate co-transporters, and therefore, should not be considered by the Board as a statement attributed to Appellants.

Error concerning "credibility" of asserted utility

In responding to Appellant's argument that the Examiner did not discuss the credibility of the asserted utility, page 16 lines 20-21 of Examiner's Answer states that "since the utility is not well established, based on the Examiner's rejection, it is also not credible." While Appellants and the Examiner disagree whether or not the claimed invention has a well-established utility (see Appeal Brief, page 12 lines 1-6), the statement that a utility that is considered not well established must also be not credible is incorrect. According to MPEP 2107.02 and the Utility Guidelines, while a well established utility must be credible, a utility that is considered not well established may still be credible (as well as specific and substantial). Therefore, the Examiner erred in stating that "the credibility of the claimed invention has been discussed in the Office Action dated 11/20/03" (Examiner's Answer at page 16, lines 21-22) and Appellants reiterate that the Examiner did **not** discuss the credibility of the utility asserted in the Specification. Appellants also argue that in light of the preponderance of evidence supporting the asserted utilities of claimed invention, the Examiner is unable to provide any factual basis to argue that the utilities are not credible to one of ordinary skill in the art.

In conclusion, based on the evidence, facts and arguments presented in the Appeal Brief and herein, Appellants request that the Board of Patent Appeals and Interferences reverse the rejection of Claim 1.

Respectfully submitted,



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